REMARKS

Amendments

Claims 2 and 29 are amended to include a second reference to angiogenesis as suggested by the Examiner. This amendment is not substantive, but merely to clarify the treatment methods should be applied to a patient in need of treatment.

Election Made With Traverse

Applicants dispute that the election was made without traverse, and direct the Examiner's attention to page 4 of the prior Response to Office Action, dated 6/20/2007. Applicants disputed that the search burden was undue, particularly where a single search of (angiogenesis) and (SEQ ID NO:1 or LL-37-receptor or FLRP1 [each of which is related]) would cover all claims.

Applicants also object to Examiner's withdrawal of claims 29-39 as drawn to a non-elected invention. Claim 29 is in fact **generic** to the elected Group II, and per MPEP 809, such generic or linking claims **must** be examined:

> The linking claims **must** be examined with, and thus are considered part of, the invention elected. When all claims directed to the elected invention are allowable, should any linking claim be allowable, the restriction requirement between the linked inventions **must** be withdrawn (emphasis added).
>
> MPEP 809 (in relevant part).

Rejection Under 35 U.S.C. § 112 for Failure of Written Description

Claims 22 and 25-27 are rejected as not complying with the written description requirement because the speciation allegedly does not "show possession" of derivatives, peptidomimetics, and mutants. Applicants dispute this characterization as follows:

First, "mutant" has a well known meaning that one or more amino acids be changed. This is clearly described in the specification at ¶ 0041, which discusses various ways to effect one or more amino acid changes in the peptide. Additionally, the claimed mutant is functionally limited to an "angiogenesis stimulating" mutant, and thus, the few amino acid changes that might

occur in such a short sequence can easily be screened for functional activity.[1] Additionally, mutants would not be allowable in a subsequent application under the KSR standards of obviousness (since a conservative amino acid change can be expected to have the same activity), and therefore they should be allowed here. Finally, failure to allow this claim means that the peptide treatment claims can easily be avoided by merely changing the terminal L to another nonpolar small amino acid such as I, M, or V, and this **trivial** modification is clearly within the scope of the invention as contemplated and described.

Second, "derivative" is a well known term, meaning that another molecular entity is added thereto. A large number of possible derivatives are clearly described at ¶ 0049. For example, a small molecule drug can be added to the peptide, or it can be pegylated[2] or lipidated, or otherwise modified to improve stability, availability or efficacy. Additionally, the derivative is functionally limited to an "angiogenesis stimulating" derivative, and thus, derivatives can easily be screened for functional activity. Additionally, such derivatives would not be allowable in a subsequent application under the KSR standards of obviousness, and therefore they should be allowed here. Finally, failure to allow this claim means that the peptide treatment claim can easily be avoided by merely glycosylating[3] or acetylating the peptide and these trivial modifications are clearly within the scope of the invention as contemplated and described.

Finally, peptidomimetic[4] means a peptide-like molecule that nonetheless lacks the peptide bond or the natural peptide side chains and are clearly described at ¶ 0047. For example, a peptidomimetic can be made by merely changing the backbone to have reduced peptide bonds or fluoridated peptide bonds, or changing L to D amino acids, thus improving stability. Additionally, the peptidomimetic is functionally limited to an "angiogenesis stimulating" peptidomimetic, and thus, peptidomimetics can easily be screened for functional activity.

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[1] See also several programs available to predict the effect that amino acid changes will have on function. *E.g.*, Pauline C. Ng and Steven Henikoffa, SIFT: predicting amino acid changes that affect protein function, Nucleic Acids Res. 31(13): 3812–3814 (2003) ("SIFT (Sorting Intolerant From Tolerant) is a program that predicts whether an amino acid substitution affects protein function so that users can prioritize substitutions for further study ").

[2] http://en.wikipedia.org/wiki/PEGylation.

[3] http://en.wikipedia.org/wiki/Glycosylation, see also http://en.wikipedia.org/wiki/Phosphorylation and http://en.wikipedia.org/wiki/Hydroxylation, as a few of the common derivatives that are easily made.

[4] http://en.wikipedia.org/wiki/Peptidomimetic.

Additionally, such peptidomimetic claims would not be allowable in a subsequent application under the KSR standards of obviousness (since the same peptide with different backbone can be predicted to have the same activity and improved stability to proteases), and therefore they should be allowed here. Finally, failure to allow this claim means that the peptide treatment claim can easily be avoided by merely making the same peptide but with reduce peptide linkages (or as a peptoid or beta-peptide), and this minor modification is clearly within the scope of the invention as contemplated and described.

Applicants have therefore pointed to the specification where derivatives, peptidomimetics, and mutants **are in fact described**, and have also provided **simple examples** of each of these modifications that are **easily within the grasp of a person of ordinary skill** in the art. Thus, Applicants assert that derivatives, peptidomimetics, and mutants are in fact in the inventors possession.

Further, the **literature confirms** that derivatives, peptidomimetics, and mutants are well within the ordinary skill in the art because it describes several variations in LL-37 that nevertheless function to bind receptor.

For example, Marja J. Nell, et al., *Development of novel LL-37 derived antimicrobial peptides with LPS and LTA neutralizing and antimicrobial activities for therapeutic application*, Peptides 27(4): 649-660 (2006) describes **thirty two different LL-37 variants** having varying levels of antimicrobial activity (see Table 1), including varying fragment lengths of the parent peptide, site specific mutants, and acetylated and amidated derivatives of LL-37. This paper provides competent evidence that is well within the skill of the art to generate mutants and derivatives of LL-37 and screen them for activity! Another **fifteen different LL-37 variants** are described and screened for activity in Marissa H. Braff, et al., *Structure-Function Relationships among Human Cathelicidin Peptides: Dissociation of Antimicrobial Properties from Host Immunostimulatory Activities*, J. Immunol. 174(7):4271-8 (2005). These variants include natural alternate fragments of the parent peptide, synthetic fragment length variants, and even an LL-37 peptide made with D amino acids! The D-form of LL-37 is a peptidomimetic, and as predicted by the inventors and well known in the art, the peptidomimetic is more resistant to peptide degradation.

Therefore, the literature already describes more than **three dozen** fragment length variants, mutants, derivatives, and peptidomimetics of LL-37 and the screening of these variants for various activities.[5] Thus, the literature proves that derivatives, peptidomimetics, and mutants are the terms having a **clear and easily understood meaning**, and that examples are **easily within the ordinary skill in the art** to make and use. Therefore, derivatives, peptidomimetics, and mutants are in fact **described** (and enabled).

If Examiner continues to assert that the making of a mutant, derivative or peptidomimetic was not conceived by inventors and that the inventors description of same is insufficient to communicate to one skilled in the art what the invention is, then Applicants request that Examiner fully articulate the rationale in **proper evidentiary form** (e.g., a declaration or affidavit) according to MPEP 2144.03, so that Applicants may properly rebut same.

Rejection Under 35 U.S.C. § 112 for Indefiniteness

Claims 22 and 25-27 are also rejected for being indefinite. However, no particular term or phrase is pointed to as having a meaning that is unclear. Instead, this rejection appears to be a re-application of the prior rejection as claiming agents that are not described. Applicants have already noted the clear meaning of the terms derivatives, peptidomimetics, and mutants. If the Examiner wishes to elaborate further on the basis for this rejection, it is requested that the Office Action be **reissued** with further clarification of the rejection to provide Applicants with an opportunity to rebut.

Rejection Under 35 U.S.C. § 102(b) by Larrick, Hirata or Chertov

Claims 2 and 22-28 are rejected as anticipated by Larrick, Hirata or Chertov, which teach the use of LL-37, but not for increasing angiogenesis. Examiner suggests limiting the claims to a patient in need of such treatment, and Applicants have made this change and thank the Examiner for the suggestion. The art is now believed to be distinguished, as none teach the LL-37 use for angiogenesis.

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[5] *See also*, Lee M.S., et al., *Serum amyloid A binding to formyl peptide receptor-like 1 induces synovial hyperplasia and angiogenesis,* J Immunol. 177(8):5585-94 (2006) (describing two non-LL-37 based peptides that bind FLRP1—an FLRP1 agonist WKYMVm and an FLRP1 antagonist WRWWWW).

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Applicants respectfully request the Examiner contact the undersigned if there are any questions. No fees are believed to be due for this submission. However, if any fees are due, the Commissioner is authorized to charge such fees or credit any overpayment to USPTO deposit account no. 50-3420, ref. 68004167-001001 (TV).

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Respectfully submitted,

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